Animal Welfare Information Center
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CONGRESS IN SESSION

by Cynthia Smith

- **H.R. 4091 To amend the Federal Food, Drug, and Cosmetic Act to revise the authority under that Act to regulate pesticide residues in food.**

Introduced March 18, 1994, by Henry A. Waxman (R-CA) and referred to the Committee on Energy and Commerce. This act may be cited as the "Pesticide Food Safety Act of 1994."

Section 408 outlines requirements for tolerances and exemptions for pesticide residues in or on food. Pesticide residue safety margins are not considered ample unless exposure per unit of body measurement is at least 100 times less than no observable effect level in animals on which the pesticide chemical residue was tested. No observable effect level is the level of exposure to a pesticide chemical that reliable data, derived from exposure of humans or animals to the pesticide chemical, demonstrate will cause no adverse effect.

- **S. 1915 To require certain Federal agencies to protect the right of private property owners.**

(cont'd p.11)

ALSO IN THIS ISSUE...

VALIDATION OF IN VITRO METHODS: REGULATORY ISSUES

by

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Introduction

The U.S. Food and Drug Administration (FDA) is primarily concerned with public safety. To that end, the use of animals in toxicity testing has played an important role in hazard/safety determination for regulated products. FDA encourages the development of alternative methods to animal testing (*e.g., in vitro* tests) and is aware that many such tests are in various stages of evolution. New laws have been enacted that either ban the use of animals in testing for certain products or mandate the development and validation of alternative methods to animal testing. Research has resulted in much activity in the development of *in vitro* methods intended for use as screens, adjuncts, and replacements for current *in vivo* standards. For example, although technical progress in the development of non-whole animal testing methods has occurred, to date, no single test, or battery of tests, has been accepted by the scientific community as a replacement to the animal model currently used in ocular irritation testing, the Draize test. For replacement of the *in vivo* standard with *in vitro* tests, further research is needed to better understand the mechanisms of action of ocular irritants *in vivo*. Criteria for the validation and acceptance of *in vitro* methodologies intended to replace *in vivo* models need to be well defined; moreover, new risk assessment paradigms to analyze information generated by *in vitro* methods need to be developed. The international community should strive for harmonization based upon consistent, science-based standards, while pursuing improved methods intended to protect public health worldwide.

The FDA Mission

The mission of the FDA is to assure the American consumer that foods are pure and wholesome, safe to eat and produced under sanitary conditions; that drugs, medical devices, and cosmetics are safe and made from appropriate ingredients; and that labeling and packaging for these products are truthful and not deceptive. The authority for this mission is issued under the following laws: 1) Federal Food, Drug, and Cosmetic Act (FFDCA) (21 U.S.C. 301-392) and its accompanying regulations and the Fair Packaging and Labeling Act (FPLA) (15 U.S.C. 1451-1461), which apply to foods and drugs for humans or animals, cosmetics, and medical devices; 2) Sections of the Public Health Service Act (PHSA)

relating to biological products for human use (42 U.S.C. 262-263) and control of communicable diseases (42 U.S.C. 264); and 3) The Radiation Control for Health and Safety Act, relating to electronic products which emit radiation, such as x rays, lasers, microwave ovens, and TV sets (42 U.S.C. 263b-263n).

Drugs, Cosmetics, and Devices Defined

A drug is an article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans and other animals and articles (other than food) intended to affect the structure or any function of the body of humans or other animals. It is the intended use which determines whether an article is a drug; therefore, foods and cosmetics may also be subject to the drug requirements of the law if therapeutic claims are made for them. The FFDCA defines cosmetics as articles intended to be applied to the human body for cleansing, beautifying, promoting attractiveness, or altering the appearance without affecting the body's structural function. A device is defined as any health care product that does not achieve any of its principal intended purposes by chemical action in or on the body or by being metabolized. The term "devices" also includes components, parts, or accessories of devices, diagnostic aids such as reagents, antibiotic sensitivity discs, and test kits for *in vitro* diagnosis of disease and other conditions (1).

Regulations and Animal Use

The FFDCA and the PHSA require manufacturers of certain consumer products to establish, before marketing, that such products meet the safety and effectiveness requirements of the law and are properly labeled. FDA regulations prescribe the type and extent of premarket testing that must be conducted, depending on the legal requirements applicable to the particular product and on the technology available to fulfill those requirements. Testing may include physical and chemical studies, non-clinical laboratory studies, and clinical tests.

Animal tests are required by FDA for drug products, vaccines, certain medical devices and electronic products, food and color additives, and new animal drugs. "Although the FFDCA does not require that cosmetic manufacturers or marketers test their products for safety, the FDA strongly urges cosmetic manufacturers to conduct whatever toxicological or other tests are appropriate to substantiate the safety of the cosmetics (2)." These tests should be state-of-the-art and generally represent consensus of the scientific community.

Regulation of Cosmetics vs. Drugs and Medical Devices

Cosmetics marketed in the United States, whether made here or imported, must comply with the FFDCA, the FPLA, and regulations issued under the authority of these laws. Unlike those products regulated by FDA that require premarket review prior to approval, there is no requirement for or against the use of animals in the substantiation of safety of the methods used by cosmetic manufacturers in testing their products. Ordinarily, a cosmetic comes under scrutiny only if a problem surfaces post-marketing. For example, if a product causes injury, such as severe ocular or dermal irritation or is otherwise shown to be deleterious to public health, the agency can require its withdrawal from the market. There appears to be a trend away from the use of animals in cosmetic testing, as many manufacturers join a growing group of those who claim to no longer use the animal model.

The application process for approval of human drugs may incorporate both *in vivo* and *in vitro* methods for toxicity testing; however, to determine efficacy or substantiate safety for products intended for use in humans, clinical trials are required for final approval of drugs and devices. Although not a regulatory requirement, the final product formulation in cosmetic testing is usually not marketed to the public until some form of limited human testing has occurred. The fundamental issue is that hazard determination and safety substantiation, although inextricably linked, are not the same. Safety is a relative concept and is achieved through a process of elimination. After all the evidence is considered, a decision is made based upon benefits of the proposed product compared to its risks.

Methods for Hazard/Safety Determination

For approximately 50 years, the rabbit has served as the model for eye and skin irritation testing (*viz.*, the Draize tests). To date, salient issues have centered around "replacement" of the Draize eye and skin tests with *in vitro* methods. Unlike drugs and medical devices, where the product may not be marketed without regulatory approval, cosmetics are presumed substantiated for safety before marketing. If this is not the case, then the sponsor of the product must communicate this fact by placing a warning statement on the label. Since a warning statement on a cosmetic label is exceedingly rare, and most likely non-existent, the consumer regards cosmetics marketed in the United States as safe. *In vitro* methods play a significant role in the toxicological evaluation of raw chemicals, therapeutic drugs, medical devices, biologicals, and cosmetics; their current application is that of screening for toxicity, especially for moderate to severe irritants, primarily as a component of a tiered testing system that seems to differ considerably "in house" depending upon the company or government to whom one may speak.

Current Utility of *In Vitro* Methods

The use of *in vitro* methods as part of different ocular irritancy testing systems was recently demonstrated in a workshop organized by the Interagency Regulatory Alternatives Group (IRAG) titled "Workshop on Eye Irritation Testing: Practical Applications of Non-Whole Animal Alternatives." Two hundred people participated in the workshop where approximately 40 laboratories from around the world submitted 55 data sets representing 23 *in vitro* methods. Expert working groups were formed to review each of the major assay systems, and their summaries were presented during the workshop. While several salient topics relevant to the status of non-whole animal methods development and use were addressed during this workshop, a significant message was clear: many companies and some governments have established alternative testing systems to help evaluate certain chemicals and products for ocular irritation potential, and *in vitro* methods are an important part of those processes.

(cont'd p.9)

THE COTTON RAT IN BIOMEDICAL RESEARCH

by

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For over a half century the cotton rat has served as a model for a remarkably extensive list of human and rodent pathogens. Currently its use is most important in studies of human respiratory syncytial virus, human adenoviruses, human parainfluenza virus type 3, and *Litomosoides carinii* (causative agent of cotton rat filariasis). In addition, it is being used in studies of the pineal gland, as a model for environmental toxicology, and as a primary animal model of human genetic therapy using the adenovirus vector. In spite of its past and present importance as well as its future potential, the model has been underutilized due to three shortcomings. First, until recently there has been no commercial source of cotton rats. Second, the lack of an inbred cotton rat has precluded important immunologic studies. Third, there have been no commercially available immunologic reagents directed against cotton rat tissues. The first two of these limitations have been overcome, as an inbred cotton rat (*Sigmodon hispidus*), developed in collaboration with Dr. Carl T. Hansen at the National Institutes of Health (NIH), is now available commercially through Virion Systems, Inc. The third limitation, the lack of immunologic reagents, is currently being addressed through a program in our laboratories, supported by a grant from the National Center for Research Resources, NIH, which will eventually result in the development of a broad library of reagents against cotton rat immunoglobulins, cellular antigens, and cytokines.

Detail of drawing by J.J. Audubon

Natural History

The cotton rat is a New World rodent, whose distribution extends from the Southern United States through Mexico, Central America, Colombia and Venezuela. In many of these regions it is the most common feral mammal, forming an important link in the food chain as well as posing occasional problems to agriculture. Seven species of cotton rats have been identified: *Sigmodon hispidus, S. alleni, S. arizonae, S. fulviventer, S. leucotis, S. mascotensis,* and *S. ochrognathis. S. hispidus* has the largest geographical distribution, extending from southern Virginia to Florida, then westward through southern Arizona, and most of Mexico, Central America, Colombia and Venezuela. It is also the ancestor of the other six species. Although there is little phenotypic difference between these species, there is striking karyotypic diversity, ranging from 22 chromosomes for *S. arizonae* to 52 for *S. hispidus*.

The Cotton Rat as a Model of Human Disease

Polio

The widespread use of the cotton rat in biomedical research began over a half century ago in the midst of an outbreak of one of the most feared infectious diseases of this century, poliomyelitis. In the latter half of the 1930's an epidemic of polio swept across the country. Although polio virus was known to cause paralytic disease in monkeys, economic and logistical problems led investigators to search for a smaller animal model. Dr. Charles Armstrong, working at the NIH in 1937, dispatched several of his workers throughout the Southern United States with instructions to live-trap and bring back to NIH any small mammals which might be adaptable to use in a laboratory setting. Many species were obtained in this manner, and all were inoculated with polio virus obtained from a fatal case in Michigan. Among the animals was one cotton rat, *S. hispidus*, and it, alone, developed paralytic disease. Following the publication of Armstrong's report in 1939, the cotton rat quickly became a widely used model for polio. By 1941 one laboratory, supported by a grant from the National Foundation for Infantile Paralysis (subsequently known as the March of Dimes), developed a breeding colony of over 1000 animals, and made these animals available to other laboratories at a cost of $0.50 each. Although the inbred mouse eventually superseded the cotton rat as a model for polio, several important advances in polio research occurred as a result of the cotton rat, detailed in over 30 published papers extending from 1939 to 1979.

Typhus

During World War II, British troops in Southeast Asia were being decimated by endemic ("scrub") typhus. A paper published in 1937 describing the susceptibility of the cotton rat to the causative agent led to a major initiative in Great Britain to develop a scrub typhus vaccine using the cotton rat. The classified project, code-named "Operation Tyburn" and directed by the Wellcome Foundation, involved the construction of an extensive animal housing facility in Sussex, the transport of cotton rats across the Atlantic in American bombers, and a large-scale breeding program designed to produce in excess of 10,000 animals per month. Although the end of the war brought Operation Tyburn to an abrupt halt, and the full utility of the vaccine was never determined, over 300,000 doses of vaccine were prepared in the facility.

Filariasis

Near the end of World War II, a report was published describing filariasis in the cotton rat, caused by an endogenous pathogen, *Litomosoides carinii*. Between 1945 and 1993 over 200 scientific papers were published describing studies of cotton rat filariasis, far more than for any other laboratory use of the cotton rat. This model contributed greatly to an understanding of the pathogenesis and immunology of filariasis and served as a primary means of testing chemotherapeutic agents.

Respiratory Syncytial Virus

Although the cotton rat is indigenous to the New World, its utility as a model for polio, typhus, and filariasis led to the establishment of breeding colonies in several European countries. In 1970, a team of Soviet scientists reported the susceptibility of the cotton rat to pulmonary infection by respiratory syncytial virus (RSV), the primary cause of infant pneumonia throughout the world. While earlier efforts in other laboratories had shown that other mammalian species were susceptible to nasal RSV infection, this group was the first to describe a small-animal model of pulmonary RSV disease. In the quarter century since this discovery, the most important contribution of the cotton rat to biomedical research has been as a model of RSV disease. Recently concluded clinical studies, which were based upon data generated in the cotton rat model, showed that human IgG with high neutralizing activity against RSV can prevent serious RSV disease in infants and children at highest risk for life-threatening disease. Further clinical trials, also based upon data generated from the cotton rat model, will determine if the same preparation will be effective in treating RSV pneumonia in infants. In addition to these studies of passive prophylaxis and therapy, ongoing studies in several laboratories to develop an RSV vaccine are relying heavily upon the cotton rat model to demonstrate both efficacy and safety.

...use of the cotton rat in biomedical research began over a half century ago in the midst of an outbreak of one of the most fearful diseases of this century, poliomyelitis.

Adenoviruses and Genetic Therapy

In 1984, Pacini and co-workers published a paper describing the pathogenesis of human adenoviruses in the cotton rat. Several subsequent papers have verified the utility of the cotton rat for the study of adenovirus pathogenesis, and have laid the groundwork for understanding the genetic basis of viral disease.

Since the cotton rat is the only small animal known to be susceptible to human adenoviruses, and since the disease produced in cotton rats is remarkably similar to that seen in humans, much of the recent work exploring genetic therapy (which employs a human adenovirus as a vector for the replacement gene) has been done in the cotton rat. The demonstration of *in vivo* expression of the cystic fibrosis transmembrane conductance regulator (CFTR) gene in the cotton rat correlated well with the subsequent pattern of expression in the cells of cystic fibrosis patients treated (*in vitro*) with the adenovirus-CFTR vector.

Care and Handling

Virion Systems, Inc., maintains two breeding colonies of cotton rats: inbred *S. hispidus* and outbred *S. fulviventer*. (The latter is in the 13th generation of an inbreeding program which, if successful, will yield an inbred strain of *S. fulviventer* within 3 years.) The two species are maintained and handled in the same manner. We have found that large polycarbonate rat cages with locking wire lids are the best form of housing. Up to five adult animals may be housed in one cage. Dietary requirements for breeding and maintenance are satisfied by standard rodent chow (4 percent ideal protein (Ed. note: commercially available rodent diets, prepared from natural products, are approximately 20 percent crude protein)) and water, with no requirements for supplements. We have tried several types of bedding, including shredded hardwood and hardwood chips, but prefer Care Fresh (Absorption Corp., Bellingham, WA), which consists of "100 percent reclaimed paper mill byproducts." We have found that this produces less dust than the other types of bedding (and cotton rats, being more active than *Mus* and *Rattus*, generate more dust), and serves as an adequate nesting material. Bedding should be changed twice weekly.

Handling cotton rats may prove unsettling to people used to dealing with *Mus* and *Rattus*. Cotton rats are <u>not</u> aggressive, although they are commonly mislabeled as such. They will, however, attempt to bite when they are picked up. Furthermore, since they move very fast, and can jump vertically over 12 inches, they pose a challenge to the novice handler. We recommend that the handler use common garden-type leather gloves. Initially, one may wish to place the cage to be changed in a deep sink to minimize the possibility of an animal escaping. In cages containing more than one animal, it is best to slide the cage top enough to reach in with the hand, but not to remove the lid, as this allows for multiple escapes. With a bit of experience and improved reflexes, most handlers will be able to change cages on a countertop.

Animals for breeding setups should be paired at the time of weaning (3-4 weeks of age), as pairing at older ages results in increased fighting. The pair should not be separated when a litter is born, as this increases the likelihood that the female

will kill the male upon reintroduction. The gestation is 27 days; inasmuch as the female goes into estrous at the time a litter is born, many breeding pairs will produce a litter each month, with an average of five pups per litter. Unlike some other rodent species (hamsters and some mouse strains, for instance), the cotton rat rarely turns on her infants due to handling. Indeed, a mother will readily accept foster infants, even if of a different age than her own litter.

...the most important contribution of the cotton rat to biomedical research has been as a model of RSV (respiratory syncytial virus) disease.

Experimental Manipulation

Cotton rats have been subjected to a wide range of experimental and surgical protocols and have proven to be a remarkably adaptable animal. The following tips may prove useful:

Anesthesia: For short-term anesthesia, we prefer methoxyflurane (Penthrane, Metofane). We use a glass instrument jar with gauze containing a small amount of anesthetic. Anesthesia is usually induced within 1 minute, and the animals remain anesthetized for about 1 minute following removal from the jar. This is adequate time for intranasal inoculation, various forms of injection, and bleeding from the retroorbital venous plexus. Neither ether nor isoflurane is acceptable, as induction times are very short and deaths are frequent.

Longer term anesthesia may be performed in two ways. For surgical procedures, induction with methoxyflurane may be followed with closely monitored maintenance using a 50 ml centrifuge tube containing methoxyflurane-soaked gauze, the opening of which is positioned near the nose of the animal. We have maintained anesthesia in this manner for up to 30 minutes with no apparent ill effects. For protocols involving administration of substances via aerosol, an alternate method is to use a mixture of ketamine HCl (25 mg/kg) and acepromazine maleate (2.5 mg/kg) given intramuscularly.

Intravenous injections: Unlike *Mus* and *Rattus*, cotton rats do not have an accessible tail vein. Substances which must be injected directly into the blood stream may be introduced via intracardiac injection into anesthetized animals. A needle (22 gauge or smaller) is introduced at a low angle slightly below the sternum and to the cardiac side of the midline, and inserted about 1.5 cm (in an adult animal). Aspiration is necessary to verify entry into the right ventricle, upon which the material may be injected. With practice, this method is as quick as tail-vein injection, and mortality in our hands is less than 1 percent.

Retroorbital bleeding: Blood samples of up to 500 ul (100 gm animal) may be obtained from anesthetized animals by inserting a Pasteur pipet about 1-2 mm, applying light pressure to the pipet at the same time it is twisted slightly to penetrate the venous plexus. While the pipet is being held with one hand, slight pressure should be applied to the jugular vein by placing the opposite thumb lightly on the neck of the animal. This will greatly increase the flow of blood into the pipet. Daily blood samples may be drawn in this manner without apparent ill effect.

Euthanasia: We have found that carbon dioxide intoxication is the preferred method of sacrificing animals, and is a method consistent with the recommendations of the Panel on Euthanasia of the American Veterinary Medical Association.

Virion Systems, Inc., can provide cotton rats of any age, although we usually ship animals at 4-6 weeks of age. Orders for up to 100 animals can generally be filled within 1-2 weeks. Although we plan to develop a large array of immunologic reagents over the next 3 years, we currently have only two reagents: polyclonal rabbit antisera against cotton rat IgG and against the C3 component of complement. Both will soon be available in purified form (IgG), with or without fluorescein isothiocyanate (FITC) labeling. We are preparing a book on the cotton rat, which will serve as a reference manual with an extensive bibliography (over 1,000 published references). However, publication of the book is still several years away, and in the meantime, we provide information from our bibliographic files on an informal basis. Further information is available from us by telephone (301-309-1844) or FAX (301-309-0471). ■

New and Updated Files From the AWIC Electronic Library

The following new files have been added to the AWIC Electronic Library:

AWA: An updated version of the Animal Welfare Act as amended (updated 3/25/94).

CAT1 and **CAT2**: The final rule and corrections of the amendment to the Animal Welfare Act regulations requiring pounds and shelters to hold and care for dogs and cats for at least 5 days (including 1 weekend day) before providing them to a dealer (*Federal Register* 58(139):39124 and 58(164):45040). Added to electronic library 4/4/94.

AVMAEUTH: *1993 Report of the AVMA Panel on Euthanasia*. This document appears in the *AWIC Electronic Library* by permission of the American Veterinary Medical Association. Added 5/27/94.

To receive the complete *Electronic Library*, send THREE(3) formatted **3 1/2" high-density** floppy disks. If you wish to update your collection, please send a single formatted 3 1/2" high-density disk. *Please specify either WordPerfect or Ascii format*. The Animal Welfare Information Center is not responsible for any alterations to the documents after downloading from AWIC computers.

Marine Mammal Welfare: The Role of USDA, APHIS

by

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Regulatory Enforcement and Animal Care

The Past

The U.S. Department of Agriculture (USDA), Animal and Plant Health Inspection Service (APHIS) was mandated by Congress to develop regulations and standards needed to enforce the Laboratory Animal Welfare Act of 1966. This was the predecessor of the current Animal Welfare Act (AWA, 7 U.S.C. §§ 2131 *et. seq.*) and the beginning of APHIS' role in enforcing its legislated provisions. As written, the AWA applies to all warmblooded animals in commerce used for research, exhibition, or the pet trade. The Secretary of Agriculture has been empowered to designate which animals and activities will be regulated. For example, retail pet stores are exempt from licensure, while wholesale trade in pet animals is regulated. Amendments to the AWA and revisions of the regulations and standards have been periodically undertaken to accommodate the expansion of covered animals and activities.

Photo by Michael Kreger

APHIS first proposed to regulate marine mammals in captivity, under the AWA, in 1978. This action was undertaken at the request of the Marine Mammal Commission (MMC), the National Marine Fisheries Service (NMFS), and organized sectors of the marine mammal industry. Regulations and standards were developed by APHIS in close association with NMFS, MMC, marine mammal exhibitors, and the American Zoo and Aquarium Association (AZA, formerly AAZPA). A Memorandum of Agreement (MOA) was signed in 1979 by APHIS, NMFS, and the U.S. Fish and Wildlife Service (F&WS). Under this agreement, AWA standards and regulations were acknowledged to be the evaluation criteria for captive care and maintenance requirements for marine mammals, and APHIS was designated to provide the inspection and enforcement workforce to implement the regulations.

Advances in scientific knowledge and husbandry practices, as well as requests from the industry, prompted a revision of the APHIS captive care and maintenance standards for marine mammals in 1984. The most prominent change made at that time was an increase in the space requirements for cetaceans (whales and dolphins). These standards are still in effect today.

The Present

MMC and NMFS requested review and revision of the 1984 regulations and standards. This process was first initiated in 1990, but a Governmentwide moratorium on regulatory changes suspended progress on this endeavor. On July 23, 1993, APHIS published an Advanced Notice of Proposed Rulemaking for the captive care and maintenance standards for marine mammals. The comment period on this advanced notice closed October 6, 1993. Thirty-seven comments were received and reviewed. These comments are being used in developing interest areas which need to be addressed during the regulatory review process.

Revision of the captive care and maintenance standards and regulations for marine mammals (9 CFR, Subchapter A, Part 3, Subpart E) is currently proceeding under the Negotiated Rulemaking (reg-neg) process. The negotiated rulemaking process is governed by the Federal Advisory Committee Act (FACA). During the first phase of this process the convener interviews potential negotiated rulemaking panel participants, formulates an issues list, and, if procceding with the reg-neg process is deemed feasible (i.e., likely to succeed), recommends a list of organizations to participate on the panel. This panel is limited by law to no more than 25 members. Expert

advisors are allowed to accompany the panel members at each session. All reg-neg sessions will be announced in the Federal Register and are open to the public. Phase 1 is currently underway, and should be completed by August 1994.

Formal reg-neg sessions are expected to begin early in fiscal year 1995. This second phase of the reg-neg process involves a facilitator to mediate the sessions in which issues and specific regulations are addressed and a consensus is reached. This consensus is used to revise or amend the appropriate regulations. A proposed rule (revised regulations and standards) is expected to be published in mid-1995. The proposed rule will undergo a comment period, and a final rule will be published after the comments have been evaluated and addressed.

In addition to the current regulations and standards review, APHIS faces several procedural and jurisdictional changes under the Marine Mammal Protection Act (MMPA) reauthorization. The MMPA was amended and reauthorized by Congress on April 25, 1994, and signed into law on April 30, 1994. MMPA amendments which affect APHIS deal primarily with captive display issues. Under the new MMPA, a NMFS permit is still required for the acquisition and holding of marine mammals for display, research, or species enhancement purposes. NMFS will continue to maintain the captive marine mammal inventory and confiscate animals when permit conditions are violated. Transfer and transport of captive marine mammals must meet the conditions set in the MMPA, and prior notification must still be given to NMFS. Sole jurisdiction over captive care and maintenance conditions and standards has been delegated to APHIS, to be administered under the AWA. Several areas which need to be addressed under the AWA regulations and standards as a result of the MMPA reauthorization include interactive programs, primarily "swim-with-the-dolphin" (SWTD) programs, animal transfer protocols for assuring AWA compliance of the receiving facility, and facility assurance of foreign facilities. Transitional procedures are being developed to implement the MMPA amendments while safeguarding the welfare of the animals.

Photo by Michael Kreger

The Future

APHIS will continue to take a leading role in the welfare of marine mammals held for display, research, and/or species enhancement. While the reauthorization of the MMPA has legislated that standards promulgated under the AWA be used as the sole regulations for care and maintenance of marine mammals in captivity, this will not significantly impact the day-to-day enforcement efforts of APHIS. This has been part of the APHIS role in marine mammal issues since the signing of the MOA in 1979. Unannounced inspections will remain the cornerstone of enforcement of the AWA. As scientific knowledge about marine mammals increases, APHIS will continue to revise the regulations and standards which protect these animals in captivity.

The future will be bringing changes, however. As previously discussed, the current regulations and standards for marine mammals under the AWA are undergoing revision. The outcome of the negotiated rulemaking process is not predictable. It is the consensus positions developed by the reg-neg panel that will provide the basis for the proposed rule. Issues which will be addressed include space requirements, psychological well-being and social grouping of animals, water quality parameters to be monitored, noise levels as they affect the animals, water temperature ranges for certain (or all) species, recordkeeping requirements, animal identification, animal transfers and transportation, interactive programs such as swim-with-the-dolphin programs, and veterinary care. The use of negotiated rulemaking to address these issues will result in strong, balanced regulations that ensure the health and well-being of marine mammals in display and research facilities. It allows APHIS to directly incorporate input from experts (scientific, academic, industry) and interested public and private organizations designed to protect these animals.

The field of animal welfare, in general, continues to make progress through increased scientific knowledge and advocacy. Consideration of psychological factors, such as environ-

mental enrichment and family/social groupings, is important to all species held in the care of humans. This includes marine mammals. APHIS is continuing to incorporate this area wherever possible into the development and revision of the animal welfare regulations. To aid in this endeavor, APHIS not only makes use of recognized experts in this field, but it is working to develop the same expertise in its own personnel.

Specifically related to the reauthorization of the MMPA, APHIS faces several immediate changes and challenges. Among the situations which were not previously covered by the AWA regulations are the SWTD programs, transfer of animals to foreign facilities, and domestic transfers of marine mammals to facilities that are in compliance with the AWA. The SWTD programs were previously regulated by NMFS through the permit criteria for these programs. APHIS is now developing an interim rule to address these programs. This interim rule is expected to be published in the Federal Register in August or September of this year. The rule will remain in effect until the publication of the final rule developed for Subpart E through the negotiated rulemaking discussed above.

Changes in the procedures and requirements for transfers of animals (both domestic and foreign) have resulted in the need for APHIS to address the issue of certifying that the receiving facilities are in compliance with the AWA and have the facilities and personnel to properly care for the animals (domestic transfers), or maintain animal care standards which are equivalent to APHIS standards (foreign transfers). The methods and protocols for developing these assurances are currently being developed.

The coming year(s) looks to be interesting and full of change. APHIS will work to obtain a balanced input from all stakeholders and interested parties in order to establish regulations and standards that ensure the continuing health and well-being of all marine mammals under its jurisdiction. ■

(For related articles see AWIC Newsletter April-June 1992 Vol. 3, No. 2.)

MARINE MAMMAL PROTECTION ACT AMENDMENTS OF 1994

P.L. 103-238

To authorize appropriations for the Marine Mammal Protection Act of 1972 and to improve the program to reduce the incidental taking of marine mammals during the course of commercial fishing operations, and for other purposes.

Introduced by Senator John Kerry (D-MA) and cosponsored by Senator Ted Stevens (R-AK) and Senator Bob Packwood (R-OR). Signed into law by President Clinton on April 30, 1994.

Some of the provisions of the law are:

...Consistent with the provisions of section 104, permits may be issued by the Secretary [of Commerce or of the Interior] for taking, and importation for purposes of scientific research, public display, photography for educational or commercial purposes, or enhancing the survival or recovery of a species or stock, or for importation of polar bear parts (other than internal organs) taken in sport hunts in Canada. Such permits, except permits issued under section 104(c)(5), may be issued if the taking or importation proposed to be made is first reviewed by the Marine Mammal Commission and the Committee of Scientific Advisors on Marine Mammals...

...A permit may be issued to take or import a marine mammal for the purpose of public display only to a person which the Secretary determines—

(i) offers a program for education or conservation purposes that is based on professionally recognized standards of the public display community;

(ii) is registered or holds a license issued under 7 U.S.C. 2131 et seq. [Animal Welfare Act]; and

(iii) maintains facilities for the public display of marine mammals that are open to the public on a regularly scheduled basis and that access to such facilities is not limited or restricted other than by charging of an admission fee...

...If the Secretary—

(i) finds in concurrence with the Secretary of Agriculture, that a person that holds a permit under this paragraph for a marine mammal, or a person exercising rights under subparagraph (C), no longer meets the requirements of subparagraph (A) (i) or (iii) and is not reasonably likely to meet those requirements in the near future, or

(ii) finds that a person that holds a permit under this paragraph for a marine mammal, or a person exercising rights under subparagraph (C), no longer meets the requirements of subparagraph (A) (i) or (iii) and is not reasonably likely to meet those requirements in the near future,

the Secretary may revoke the permit in accordance with section 104(e), seize the marine mammal, or cooperate with other persons authorized to hold marine mammals under this Act for disposition of the marine mammal. The Secretary may recover from the person expenses incurred by the Secretary for that seizure....

cont'd from p.2

In Vitro Testing Methods and Regulatory Acceptance

Certain external influences (3,4) are driving change that will most likely result in *in vitro* methodologies occupying a more prominent place in toxicity testing. The cosmetic industry, in particular, is looking to Federal agencies for guidelines identifying regulatory acceptance criteria for submitting data generated from *in vitro* methods intended to at least partially replace some data that, heretofore, originated from *in vivo* testing. Although specific criteria for regulatory acceptance of *in vitro* models have not yet been published, validation of a proposed model may be considered an important criterion in this process.

Although validation of new methods is not a primary responsibility for regulatory agencies, validation by the scientific community may be considered pivotal to regulatory acceptance. However, "validation" of a method does not necessarily guarantee regulatory acceptance. Like pre-market approval of regulated products, the acceptance criteria of a proposed new method will largely be determined by the sponsor's claim for the test. As part of the review of a proposed *in vitro* method during the risk assessment process, new data need to be evaluated, and herein lies a formidable challenge; *viz*., new standards of data comparison need to be considered.

When an *in vitro* method is proposed to test for an *in vivo* response, such as dermal or ocular irritation, the qualitative data generated by the test as compared to the *in vivo* standard are imperative. In other words, what are the endpoints and how do they relate to the tissues evaluated by the Draize. For example, discussion often centers around the empirical vs. mechanistic approach. A correlative (empirical) method, which may successfully identify a severe dermal or ocular irritant early in the evaluative stages of testing, may be acceptable to the regulatory agency as a screen, but since it does not predict safety, would be inadequate as a replacement. However, for a method to successfully identify a severe irritant with an acceptable level of false positives (substantiate hazard/high sensitivity) and predict safety with a low incidence of false negatives (substantiate safety/high specificity), a full understanding of the mechanism by which the technique detects irritation in a specific tissue appears to be essential to replacement (3).

In Vivo "Replacement"

What, then, needs to be accomplished by the scientific community to advance the acceptance of new techniques? For true replacement of an *in vivo* with an *in vitro* model to successfully occur, research should focus on the mechanisms of dermal or ocular irritation in humans. It appears, therefore, that methods development targeted for replacement will need to successfully predict the presence or absence of irritation at the physiological, anatomical, biochemical, or molecular level of tissue pathology. Tissue repair, the reversibility of lesions, is an important facet in classification of substances; moreover, in the review of FDA-regulated substances, those products that cause irreversible damage to some tissues would be less likely to receive approval. Similarly, some products may not cause severe tissue damage or visible irritation upon exposure but may cause considerable discomfort or pain. Demonstrating such phenomena will be most difficult without *in vivo* modeling. These examples highlight formidable challenges that need to be addressed as issues germane to total replacement are identified and explored.

As we try to envision replacement of the animal model in the context of safety substantiation, several considerations clearly need to be addressed. Few would accept the simplistic notion of total replacement of an animal model, such as the Draize, with a single *in vitro* test. A risk assessment system that replaces an animal model will necessarily consist of a multidisciplinary approach that incorporates information from several sources in a systematic or tiered approach.

The Tiered Approach to Substance Testing

The first level will be that of reviewing information already known about the particular class in which the substance resides. It is important to note here that much of the historical information is derived from *in vivo* testing such as dose response relationships as well as toxicokinetic and toxicodynamic data. Other sources include structure activity relationships and known physical-chemical properties of the class from which the substance is derived. The next tier in the system may consist of a battery of assays, each measuring various mechanisms of dermal or ocular irritation. Finally, a decision point is reached; if there is sufficient evidence that the substance is a severe irritant, it may be classified. If insufficient information exists to classify, then further *in vivo* data are required. As methods are examined for their role in irritation testing, a standardized validation paradigm must be developed. A framework for such a model was reported in ATLA (6) from the CAAT (7)/ERGATT (8) Workshop and proposed by the Johns Hopkins University Center for Alternatives to Animal Testing (9).

Components of Methods Evaluation

As a validation paradigm is considered, the protocol and the data generated by the study are of particular importance for serious evaluation. The protocol for an *in vitro* method should clearly identify the *in vivo* endpoints, and the data generated from the test should provide information relevant to these endpoints. Once *in vitro* data have been accumulated, the standard to which they will be compared is extremely important. To that end, careful consideration must be given to the guidelines established for *in vitro-in vivo* data comparisons. Currently, this is established on a case-by-case basis with FDA-regulated products. Until a model for risk assessment based upon *in vitro* data is developed, there must be adequate means of comparing the results of our tests with known *in vivo* outcomes.

From a regulatory perspective, the following precepts should be considered as guidelines of the scientific process for validation testing of proposed methodologies:

- Define the mechanistic relevance of the *in vitro* test endpoint to effects observed *in vivo*.
- Determine the relationship between the known *in vivo* dermal or ocular irritation potential of the test substance and the *in vitro* test results.
- Demonstrate the quality of the *in vitro* data by evaluating the method's protocol, intra-laboratory repeatability, inter-laboratory reproducibility, number and type of chemicals used, and adherence to GLP (10) standards.

- Define potential uses and limitations of the alternative method including type or class of chemical to which it has application and how the data might be used for practical safety or hazard determinations (11).
- For new molecular entities with no history of previous testing, animal data will have to validate any *in vitro* testing system for that class of compounds.

The following expands upon nomenclature germane to new methods development, validation, and regulatory acceptance:

- *Sensitivity* is the ability of the proposed method to detect that proportion of those compounds tested that are truly positive as an irritant or toxicant. Although a high sensitivity is important in any risk assessment scheme, false positives in sensitivity testing error toward the conservative and, therefore, do not present the unfavorable consequences that may occur with false negatives in specificity testing.
- *Specificity* is the ability of the proposed method to detect those compounds tested that are truly negative as an irritant or toxicant. False negatives in specificity testing mean truly positive substances fail to be detected, thus, allowing a potential toxicant to be classified incorrectly and inadvertently allowed for human/animal use. Clearly, a high specificity is extremely important from a regulatory perspective.
- *Predictive Value* in screening tests is the probability that a positive test is truly positive and a negative test is truly negative.
- *Precision* is the quality of being sharply defined or stated (*e.g.*, the number of distinguishable alternatives from which a measurement was selected). An example of precision would be the standard deviation or comparing the standard deviation to the mean or the coefficient of variation (12).
- *Repeatability* is the ability of the results of a testing method to perform consistently when conducted several times within a particular laboratory. The standard deviation may be employed as a measurement of precision when considering repeatability.
- *Ruggedness* or *rigor* refers to the method's ability to achieve a suitable degree of repeatability in the sponsor's laboratory. Without ruggedness or rigor, a method would not be expected to perform adequately in different laboratories.
- *Reproducibility* is the ability of the results of a testing method to perform consistently when conducted in different laboratory settings. The standard deviation may be employed as a measurement of precision when considering reproducibility.
- *Bias* is the deviation of results or inferences from the truth or processes leading to such deviation. Bias may occur when any trend in the collection, analysis, interpretation, publication, or review of the data leads to conclusions that are systematically different from the truth. There are many sources of bias including flawed study design, data collection, statistical summary data, data analysis or interpretation, instrumental error, handling of outliers, and prejudice in study procedures that lead to one-sidedness in any facet of a study (13).

Summary

Many challenges face stakeholders now and in the future for risk assessment in the area of toxicity testing. The notion of replacement will vary considerably depending upon many variables. Particularly cogent at this time is the need to identify criteria for both the comparison of *in vitro* with *in vivo* data and regulatory acceptance for *in vitro* methods intended to replace the animal model in toxicity testing. The transition from comparing *in vitro* data to the animal standard to that of a "Gold Standard" is complex and will require the implementation of a novel risk assessment paradigm. Validation of *in vitro* methods needs to adhere to the scientific precepts of purpose and endpoint identification, correlative vs. mechanistic basis, intralaboratory reproducibility, interlaboratory repeatability, protocol standardization, technology transfer, chemical reference standardization, data base development and quality control/quality assessment through GLP-like standards. Finally, this necessarily requires an international effort to coordinate and harmonize the multifaceted issues in risk assessment for hazard/safety determination.

To obtain additional information, Dr. Wilcox may be contacted at 301-594-1798 (301-594-1830 FAX) or by writing to the Office of Animal Care and Use, U.S. Food and Drug Administration, Center for Veterinary Medicine, MPN-2, HFV-4, 7500 Standish Place, Rockville, MD 20855.

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Legislation cont'd from p.1

Introduced March 9, 1994, by Richard C. Shelby (D-AL) and referred to the Committee on Environment and Public Works. This act may be cited as the "Private Property Owners Bill of Rights."

Congress finds that the Endangered Species Act of 1973 (1 U.S.C. 1531 et seq.) and section 404 of the Federal Water Pollution Control Act (33 U.S.C. 1344) have been implemented in a manner that deprives private property owners of the use and control of their property. As additional Federal programs are proposed that would limit and restrict the use of private property to provide habitat for plant and animal species, the rights of private property owners must be recognized and respected. Section 7 amends the Endangered Species Act of 1973 (16 U.S.C. 1540) to allow private property owners the right to appeal the following actions: determination that a parcel of property is critical habitat for a species; denial of a permit for an incidental take; and imposition of an order prohibiting or substantially limiting the use of the property. Section 8 outlines procedures for private property owners to gain compensation for property set aside as a result of a Federal agency's decision. Related bills: H.R. 3875, June 1994; H.R. 3997, March 1994; S. 1440, August 1993; S. 1521, October 1993; H.R. 1490, March 1993; S. 3159, August 1992; H.R. 4045, November 1991.

- **H.R. 3575 To amend title 18, United States Code, to provide more complete protection to animal enterprises and the people associated with them.**

Introduced on November 19, 1993, by Charles W. Stenholm (R-TX) and referred to the Committee on the Judiciary. This act may be cited as the "Animal Enterprise Protection Act of 1993."

Chapter 13 of title 18, United States Code, is amended by adding the following: Whoever by force, threat of force, or physical obstruction, intentionally injures, intimidates, or interferes with any person, or attempts to do so, because that person is engaging in activities in an animal enterprise; or intentionally damages or destroys the property of a facility , or attempts to do so, because that facility is an animal enterprise shall be punished. An "animal enterprise" is defined as a commercial or academic enterprise that uses animals for food or fiber production, agriculture, research, testing, a zoo, aquarium, circus, rodeo, lawful competitive animal event, and any fair or similar event intended to advance agriculture. Penalties for violation include in the case of a first offense a fine and imprisonment for not more than 1 year, in the case of a second or subsequent offense after a prior conviction, a fine and imprisonment for not more than 3 years. If bodily injury results then the length of imprisonment shall be not more than 10 years, and if death results, it shall be for any term of years or for life. Related bills and laws: H.R. 3064, September 1993; P.L. 102-346, August 1992.

- **H.R. 4044 To require the Secretary of Agriculture to issue regulations for the purchase and eradication of swine infected with or exposed to brucellosis.**

Introduced March 16, 1994, by Martin H. Lancaster (R-NC) and referred to the Committee on Agriculture.

Not later than 30 days after the date of the enactment of this act, the Secretary of Agriculture shall issue regulations that authorize the Secretary to purchase and eradicate, in accordance with section 11 of the Act of May 29, 1884 (21 U.S.C. 114a), swine infected with or exposed to brucellosis. Related bill. S. 1901, 1994.

- **Public Law 103-182 To implement the North American Free Trade Agreement**

This act may be cited as the "North American Free Trade Agreement Implementation Act."

Passed December 8, 1993. Part 2, section 361, outlines agricultural, technical and conforming amendments governing importation and inspection of animals, and amendments to the Poultry Products Inspection Act (21 U.S.C. 466(d)) and Federal Meat Inspection Act (21 U.S.C. 620(e)). The Secretary of Agriculture shall make a grant to a land-grant college for the construction of a facility for the conduct of research in animal health, disease-transmitting insects, and toxic chemicals that require the use of a biocontainment facility. To be eligible for the grant, the land- grant college must be adjacent to the international border with Mexico and have an established program in animal health research. The facility constructed with the grant shall be known as the "Southwest Regional Animal Health Biocontainment Facility."

- **H.R. 4008 To authorize appropriations for the National Oceanic and Atmospheric Administration for fiscal years 1994 and 1995, and for other purposes.**

Introduced by Solomon P. Ortiz (R-TX) on March 10, 1994, and referred to the Committee on Merchant Marine and Fisheries. Section 101(d) authorizes the Secretary of Commerce to enable the National Oceanic and Atmospheric Administration to carry out the Coastal Ocean Program. A total of $200,000 is available until expended to study the use of oceanic data obtained from satellite imagery and other sources to determine and predict the presence of endangered sea turtles in the Gulf of Mexico

- **S.2100 To provide for rural development, multiple-use management, expenditures under the Knustson-Vandenburg Act of 1930, and ecosystem-based management of certain forest lands, and for other purposes.**

Introduced May 10, 1994, by Dennis DeConcini (D-AZ), and read and passed. This act may be cited as the "Stewardship End-Result Contracts Demonstration Act."

Section 3 authorizes the Secretary of Agriculture to apply all or part of revenues received from timber to be used for site preparation, replanting, silviculture programs, recreation and wildlife habitat.

- **S.2142 To designate certain lands in the Commonwealth of Virginia as a National Scenic Area for protection of the watershed and scenic values, recreation use, protection of wildlife and their habitat, and for other purposes.**

Introduced May 23, 1994, by John W. Warner (R-VA) and referred to the Committee on Agriculture, Nutrition, and Forestry. This act may be cited as the "Mount Pleasant National Scenic Area Act."

The purposes of this act are to ensure appropriate protection and preservation of the scenic quality, water quality, natural characteristics, and water resources of the Mount Pleasant National Scenic Area; to protect and manage vegetation to provide wildlife and fish habitat; and to encourage old-growth forest development.

- **H.R. 4289 To amend the Watershed Protection and Flood Prevention Act to establish a Waterways Restoration Program, and for other purposes.**

Introduced April 21, 1994, by Elizabeth Furse (R-OR) and referred jointly to the Committees on Agriculture, Merchant Marine and Fisheries, and Public Works and Transportation. This act may be cited as the "Waterways Restoration Act of 1994."

Congress finds that protecting and restoring watersheds provides critical ecological benefits by restoring and maintaining biodiversity, providing fish and wildlife habitat, filtering pollutants, and performing other important ecological functions.

- **H.R. 3978 To amend the Endangered Species Act of 1973 to provide for the conservation of threatened species and endangered species, to assure balanced consideration of scientific, economic, and social factors in the implementation of the act, to provide private property protections, to remove obsolete provisions, and for other purposes.**

Introduced March 8, 1994, by Richard W. Pombo (R-CA) and referred to the Committee on Merchant Marine and Fisheries. This act may be cited as the "Endangered Species Management Act of 1994."

The purposes of this act are to provide a practical means whereby ecosystems upon which endangered and threatened species directly depend may be conserved, and to provide programs for the conservation of endangered species and threatened species that take into account economic and social consequences.

The Secretary of the Interior may not list a species as endangered or threatened unless a report has been prepared that includes a complete file of scientific data and collection methodology used to determine the listing, and a recovery plan for the species that includes scientific data and projected costs. The report must be reviewed by a scientific peer review panel. The Secretary of the Interior must submit an intent to list a species as endangered or threatened to a newspaper of general circulation in the State where the species is believed to occur for 5 consecutive days. Public hearings must also be held in the State where the species resides. Related bills: H.R. 3997, March 1994; S. 1440, August 1993; S. 1521, October 1993; H.R. 1490, March 1993; S. 3159, August 1992; H.R. 4045, November 1991.

- **H.R. 3987 To provide for conservation of rhinoceros and tigers.**

Introduced March 9, 1994, by Jack Fields (R-TX) and referred jointly to the Committees on Merchant Marine and Fisheries and Ways and Means. This act may be cited as the "Rhinoceros and Tiger Conservation Act of 1994."

Congress finds that the world's rhinoceros population is declining at an alarming rate, a 90-percent decline since 1970. The purposes of this act are to assist in the conservation of rhinoceros and tigers by supporting the conservation programs of nations whose activities affect rhinoceros and tiger populations, and to provide financial resources for those programs.

- **H.R. 3997 To amend the Endangered Species Act of 1973 to require the preparation of economic impact analyses with respect to certain actions to protect endangered species and threatened species, and for other purposes.**

Introduced March 10, 1994, by John T. Doolittle (R-CA) and referred to the Committee on Merchant Marine and Fisheries. This act may be cited as the "Balanced Economic and Environmental Priorities Act of 1994."

Section 4 of the Endangered Species Act of 1973 (16 U.S.C. 1533) is amended to include a section on economic impact analysis. An officer or employee of a Federal agency shall not implement or enforce a designation, regulation, or recovery plan unless the Secretary [of the Interior] has prepared an economic impact analysis. The economic impact analysis shall include determination of the following: identifiable and potential job losses; identifiable losses in the value of real property resulting from implementation and enforcement; and losses in business enterprises. Compensation shall be paid to persons who incur economic loss as a result of a species being listed as an endangered or threatened species. Related bills: H.R. 3978, March 1994; S. 1440, August 1993; S. 1521, October 1993; H.R. 1490, March 1993; S. 3159, August 1992; H.R. 4045, November 1991.

- **H.R. 3954 To expand the Mni Wiconi Rural Water Supply Project, and for other purposes.**

Introduced March 3, 1994, by Tim Johnson (R-SD) and referred to the Committee on Natural Resources. This act may be cited as the "Mni Wiconi Act Amendments of 1994."

Congress finds that the lack of water supplies on the Rosebud Reservation and Lower Brule Reservation restricts efforts to promote economic development of those reservations. The Secretary [of the Interior] is authorized and directed to plan, design, construct, operate maintain, and replace a municipal, rural and industrial water system. The Secretary shall make Federal grants to the Oglala Sioux, Rosebud Sioux, and Lower Brule Sioux Bio-Diversity Trusts. Each trust shall be eligible for Federal grants if it selects and provides funding to projects which restore, protect, and enhance wildlife and wildlife habitat.

- **S. 1831 To implement the Protocol on Environmental Protection to the Antarctic Treaty, to enact a prohibition against Antarctic mineral resource activities, and for other purposes.**

Introduced February 7, 1994, by Claiborne Pell (D-RI) and referred to the Committee on Foreign Relations. This act may be cited as the "Antarctic Environmental Protection Act of 1994."

Congress finds that the Antarctic Treaty and the Protocol on Environmental Protection to the Antarctic Treaty serve important U.S. environmental and resource management interests, while at the same time preserving the freedom of scientific investigation in Antarctica. Activities in Antarctica are to be planned and conducted so as to limit adverse impacts on the environment and dependent ecosystems. Section 4 outlines prohibited acts such as: disposing of wastes from land into the sea of Antarctica; introducing species of animals or plants not indigenous to Antarctica; killing, injuring, capturing, handling, or molesting any native mammal or bird; removing or damaging native plants such that their distribution or abundance would be affected; and flying or landing helicopters or other aircraft in a manner that disturbs concentrations of birds and seals. Related bills: S.1427, August 1993; S. 3189, August 1992.

- **H.R. 3526 To end the use of steel jaw leghold traps on animals in the United States.**

Introduced November 17, 1993, by Nina M. Lowey (R-NY) and referred to the Committee on Energy and Commerce.

It is the policy of the United States to end the needless maiming and suffering inflicted upon animals through the use of steel jaw leghold traps by prohibiting the shipment in interstate or foreign commerce of the traps and of articles of fur from animals that were trapped in the traps. It is unlawful for any person to knowingly import, export, ship, or receive any article of fur from an animal trapped in a steel jaw leghold trap; or to deliver, carry, transport, ship, sell, receive, acquire, or purchase any steel jaw leghold trap. Related bills: S. 1343, August 1993; H.R. 1354, March 1991; H.R. 4604, April 1990; S. 2239, March 1982. ■

THE IMPORTANCE OF ANIMALS IN BIOMEDICAL AND BEHAVIORAL RESEARCH

A Statement from the Public Health Service, U.S. Department of Health and Human Services

Virtually every medical achievement of the last century has depended directly or indirectly on research with animals. The knowledge gained from animal research has extended human life and made it healthier through many significant achievements, as illustrated by the following examples: vaccines to prevent poliomyelitis and other communicable diseases; surgical procedures to replace diseased heart valves; corneal transplants to restore normal vision; new medicines to control high blood pressure and reduce death from stroke; antipsychotic drugs to treat mental disorders; broad spectrum antibiotics to treat infections; and chemical agents to cure or slow childhood cancers. Of course, there are many other diseases and disorders, such as AIDS, many forms of cancer, common cold, Alzheimer's disease, schizophrenia, hepatitis, arthritis, cystic fibrosis, and brain and spinal cord injuries—just to name a few—for which either no effective prevention, treatment, or cure now exists.

The use of living animals remains an important way to solve a medical problem. Researchers continually seek other models to understand the human organism, study disease processes, and test new therapies. In seeking more rapid and less expensive ways to obtain basic biological information that can be applied to human disease, scientists often study simpler organisms, such as bacteria, yeasts, roundworms, fruit flies, squids, and fishes. Researchers have spent decades learning how to sustain cells, tissues, and organs from both animals and humans outside the body to understand biological processes and develop new medical treatments. Mathematical, computer, and physical models complement animal experimentation as well. Although computers alone cannot produce new biological information, they enable scientists to analyze vast amounts of data and test ideas. In the end, the validity of the results obtained from these model systems must be verified in appropriate animal systems and, possibly as the final step, in clinical trials using human volunteers.

Like most people, scientists are concerned about animal well-being. Elaborate safeguards in the form of Federal laws have been implemented to ensure that institutions comply with the regulations and policies affecting the care and use of animals in research. Before beginning a project, all research proposals involving animals must be carefully reviewed and approved at each research facility by an Institutional Animal Care and Use Committee comprised of scientists, veterinarians, and private citizens. Veterinarians trained in laboratory animal medicine are responsible for observing and caring for animals, providing guidance to researchers, and overseeing institutional animal care programs. In addition, institutions conducting animal research are routinely inspected by the U.S. Department of Agriculture and monitored by the U.S. Public Health Service. Many institutions are further accredited by an independent evaluating body, the American Association for Accreditation of Laboratory Animal Care.

For more than a century, there have been organized groups and individuals who have objected to using animals in biomedical research. This opposition has increased markedly in the last two decades. Animal activist organizations spurred by a philosophy that there is no moral justification for the use of animals in research—even to save human lives—have attempted to slow or halt the work of scientists. Some disseminate misleading information, intimidate or harass individual scientists, conduct mass demonstrations, or even commit acts of vandalism or terrorism. The few health professionals who support the activist movement stand apart from the vast majority of the Nation's physicians, and most Americans readily accept the fact that animal research is necessary to achieve medical progress.

Institutions receiving support from the Public Health Service are obliged to adhere to the highest possible standards for the humane care and responsible use of laboratory animals. And scientists themselves have adopted the principle: "Good Animal Care and Good Science Go Hand in Hand."

Announcements...

• ANIMAL CARE SYMPOSIUM PROCEEDINGS PUBLISHED

The Johns Hopkins School of Public Health, Office for Research Subjects published *Symposium Proceedings: Animal Care and Use Committees and Alternatives*. The proceedings from the symposium held in Baltimore on June 18, 1992, addresses concepts of alternatives, research models using various alternatives, resource information, regulatory requirements for alternatives as an ethical issue for Institutional Animal Care and Use Committees (IACUCs), the role of IACUCs in pre-college education, and the presentation "What is a Moral Mandate?" The publication is available from Johns Hopkins School of Public Health, Office for Research Subjects. Contact Joan Polling at (410) 955-3193 or FAX (410) 955-0258 for ordering information.

• NEW PUBLICATIONS FROM THE UNIVERSITIES FEDERATION FOR ANIMAL WELFARE

Modified Cages for Laying Hens is the 102-page proceedings of a 1993 symposium on improving the battery cage with regard to poultry welfare. Edited by C.M. Sherwin, the paperback book contains scientific studies that evaluate modified (or enriched) cages as a short-term alternative to intensive housing of hens in battery cages. Modifications studied include providing a perch, increasing/changing the cage dimensions, and providing a nest box or dust-bath. The cost is £8 or U.S. $18 (post free).

UFAW has also published two booklets on animal experimentation and welfare. The 25-page paperback *The Use of Animals in Scientific Procedures* by Frances Kim discusses animal numbers used in experimentation, rationale for use, legislation, toxicity testing, and welfare. It is primarily geared toward undergraduate students. The cost is £1.50 or U.S. $4 (post- free). The eight page leaflet *Animal Experiments* is also designed for students and answers questions about animal numbers, the justification for animal research, and typical scientific procedures involved. The cost is £0.50 or U.S. $1.25.

For additional information contact UFAW, 8 Hamilton Close, South Mimms, Potters Bar, Herts EN6 3QD, UK, Tel: +44-707-658202, FAX: +44-707-649279.

• LABORATORY ANIMAL ANESTHESIA WORKSHOP

In conjunction with the 5th International Congress of Veterinary Anesthesia, an adjunct workshop devoted to laboratory animal anesthesia will be held at the Ontario Veterinary College, University of Guelph on August 25-26, 1994.

The first day's session will be at the International Congress and will include talks by Dr. Paul Flecknell on "Recent Advances in the Recognition and Treatment of Pain in Laboratory and Domestic Animals," and by Dr. Ted Stanley on "Anesthesia in the Future." Dr. Flecknell will also moderate short paper presentations and group discussions. The second day will be devoted to wet lab sessions where attendees will participate in practical anesthetic techniques.

The lecture and workshop short course have limited enrollment. The intended audience is researchers, veterinarians, technicians, and individuals responsible for laboratory animal care and well-being in a teaching/research setting. For more information, contact Lifelearn V Inc., MacNabb House, University of Guelph, Guelph, Ontario, N1G 2W1, Tel: (519) 767-5043, FAX: (519) 767-1101, e-mail: rnigol@ovcnet.uoguelph.ca.

• NIH ANIMAL WELFARE EDUCATION WORKSHOPS

The National Institutes of Health (NIH), Office of Extramural Affairs (OER), Office for Protection from Research Risks (OPRR) is cosponsoring a National Animal Welfare Education Workshop with Louisiana State University Medical Center and Xavier University of Louisiana. The workshop is open to all persons involved in the management and/or oversight of an institutional animal care and use program including institutional administrators, members of Institutional Animal Care and Use Committees, laboratory animal veterinarians, investigators, and technicians. The workshop will address such issues as: 1) adequacy of computer searches for alternatives; 2) NIH, USDA, and FDA alternatives initiatives; 3) occupational health—implementation, update, and biosafety concerns; and 4) the roles of animals and alternatives in education. It will be held on September 29-30, 1994 at the Monteleone Hotel, New Orleans, LA,

The general registration fee is $150. For more information, contact Lois Herbez, Administrative Secretary, Louisiana State University Medical Center, 1542 Tulane Ave., New Orleans, LA 70112, Tel: (504) 568-4198 or Fax: (504) 568-4843.

The NIH, OER, OPRR is also cosponsoring a workshop with the Medical University of South Carolina. The theme of this workshop is "New Frontiers in Surgery". This program, to be held at the Sheraton Charleston Hotel ((803) 723-3000), Charleston, SC, on December 1-2, 1994, will address ethics, protocol review, and technical and training aspects related to new surgical and interventional technologies. Topics to be discussed include xenographic procedures, fetal intervention, transgenic technologies, and use of biomaterials in orthopedic surgery.

The registration fee is $150 before November 15, 1994 and $175 after November 15, 1994. For more information, contact Michael Swindle, DVM, MUSC/Comparative Medicine, 171 Ashley Ave., Charleston, SC 29425-2211, Tel: (803) 792-3625 or Fax: (803) 792-9067.

• SCAW TO SPONSOR SEMINAR AT NATIONAL AALAS ON "THE HUSBANDRY AND CARE OF BIRDS IN THE LABORATORY"

The Scientists Center for Animal Welfare (SCAW) will sponsor a seminar on "**The Husbandry and Care of Birds in the Laboratory**" at the American Association for Laboratory Animal Science's (AALAS) 45th Annual Meeting in Pittsburgh, Pennsylvania on October 20, 1994 from 2 to 5 P.M.

This seminar will address issues concerning the well-being of many bird species used in the laboratory and in field

research. Current regulations and guidelines do not always provide enough guidance to investigators, animal care givers, and Animal Care and Use Committees. Some species to be covered will include raptors, passerines, poultry, psittacines, pigeons, and quail.

The Chair of the seminar is Joy A. Mench, DPhil, SCAW Advisory Board Member and Associate Professor, Department of Poultry Science, University of Maryland.

Researchers, regulatory personnel, members of Animal Care and Use Committees, administrators, and others interested in these issues are encouraged to attend. For more information contact: SCAW, Golden Triangle Building One, 7833 Walker Dr., Suite 340, Greenbelt, MD 20770, Tel: (301) 345-3500, FAX: (301) 345-3503 for program information or Betty Cartwright at AALAS for registration information, Tel: (901) 754-8620.

• SCAW AND UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT SAN ANTONIO CO-SPONSOR CONFERENCE

The Scientists Center for Animal Welfare (SCAW) and the University of Texas Health Science Center at San Antonio will co-sponsor a two-day conference on "Current Issues and New Frontiers in Animal Research" in San Antonio, Texas, on December 8-9, 1994. The Co-chairs are: Ernest D. Prentice, PhD, University of Nebraska Medical Center; Kathryn A.L. Bayne, DVM, PhD, DipACLAM, AAALAC; and Molly Greene, University of Texas Health Science Center at San Antonio.

Three sessions will address different general issues. Topics about IACUCs will include:

- USDA Update on Regulations and Litigation
- Protocol Review: Too Much Paperwork?
- Other IACUC Protocol Review Issues
- How and Why Should IACUCs Develop a Code of Ethics
- Confidentiality and the IACUC: Legal, Ethical, and Practical Issues
- Why Should Anyone Want To Be an Unaffiliated Member of an IACUC?
- Biotechnology's Effect on IACUCs

Topics in the second session on "Biocontainment, Biosafety and Biohazards" will include:

- Enrichment and Biocontainment Issues
- Biocontainment Research
- Biosafety Issues
- Methods of Biocontainment

The third and final session is entitled "New Frontiers" and will include:

- Zoonosis: What You Need to Know Now and in the Twenty-first Century
- Lab Animal Behavior: New Developments and Future Areas of Interest
- Opportunities for Alternatives at the University Level
- Xenotransplantation: Justifiable Clinical Research or Medical Adventurism?

Researchers, regulatory personnel, members of Animal Care and Use Committees, administrators, and others interested in these issues are encouraged to attend. For more information contact: SCAW, Golden Triangle Building One, 7833 Walker Dr., Suite 340, Greenbelt, MD 20770, Tel: (301) 345-3500, FAX: (301) 345-3503.

• LABORATORY RAT AND MOUSE HOUSING PUBLICATION AVAILABLE

Evaluation of Housing Conditions for Laboratory Mice and Rats: The Use of Preference Tests for Studying Choice Behavior by Dr. Harry J.M. Blom covers description and validation of preference test systems, cage height, light intensity, bedding material, floor type, mouse preference for clean versus soiled cages, and cage thermal preferences. The 138-page paperback is available for $15 from the Department of Laboratory Animal Science, P.O. Box 80,766, 3508 TD Utrecht, The Netherlands.

• THE SHAPE OF ENRICHMENT

The Shape of Enrichment newsletter is dedicated to sharing ideas, inspirations, and practical knowledge of environmental and behavioral enrichment strategies among those working in the field of animal care. It is an open forum for keepers, trainers, curators, researchers, administrators, exhibit designers, volunteers, and anyone else interested to exchange techniques and approaches to captive enrichment. All submissions are welcome, from feature-length articles to short blurbs.

The Shape of Enrichment is published quarterly. Subscriptions are $12 per calendar year, payable in U.S. funds only, drawn on a U.S. bank. Mid-year subscriptions are prorated. Back issues are available for $3 each. Send all subscription requests, article submissions, letters, comments, and questions to: Valerie J. Hare, Karen E. Worley, Editors, Shape of Enrichment, 1650 Minden Dr., San Diego, CA 92111-7124, Tel: (619) 231-1515, ext. 4272, FAX: (619) 279-4208. ■

GRANTS FROM THE SMALL BUSINESS INNOVATION RESEARCH PROGRAM

The National Institutes of Health, Centers for Disease Control and Prevention, and the Food and Drug Administration are offering funding through the Small Business Innovation Research program for support of research and development of new technologies and methodologies that have the potential to succeed as commercial products. This program is open to small business concerns as well as to scientists at research institutions, including colleges and universities. Eligibility requirements, definitions, application procedures, review considerations, application forms and instructions, and other information are contained in the *Omnibus Solicitation of the Public Health Service for Small Business Innovation Research (SBIR) Grant and Cooperative Agreement Applications* available from MTL, Inc., 13687 Baltimore Ave., Laurel, MD 20707, Tel: (301) 206-9385, FAX: (301) 206-9722.

Upcoming Meetings

1994 ChimpanZoo Conference, the Jane Goodall Institute and ChimpanZoo, September 17-21, 1994. West Palm Beach, FL. Contact: (215) 895-1645 - Virginia Landau.

1994 AZA Conference, American Zoo and Aquarium Association, September 18-22, 1994. Atlanta, GA. Contact: (304) 242-2160.

The Association of Avian Veterinarians' 15th Annual Conference, September 27-October 1, 1994. Reno, NV. Contact: (303) 756-8380.

The Conference 1994, American Humane Association, September 28-October 1, 1994. New Orleans, LA. Contact: (800) 277-4645.

Use of Animals in Research and Alternatives, National Institutes of Health, Office of Protection from Research Risks, September 29-30, 1994. New Orleans, LA. Contact: (504) 568-4198 - Lois Herbez.

1994 American Association of Zoo Keepers National Conference, October 9-13, 1994. Omaha, NE. Contact: (402) 733-8401 - Diane Callaway or Lisa Cuevas..

European Marmoset Research Group, 1st General Assembly, November, 1994 (no date specified). Paris, France. Contact: Christopher Pryce, Anthropologisches Institut, Universiat Zurich-Irchel, Winterthurerstrasse 190, CH-8057 Zurich, Switzerland.

New Frontiers in Surgery, National Institutes of Health, Office of Protection from Research Risks, December 1-2, 1994. Charleston, SC. Contact: (803) 792-3625 - M. Michael Swindle, DVM.

Society for Conservation Biology, June 7-11, 1995. Fort Collins, CO. Contact: (303) 491-6714 - Richard Knight, Dept. of Fishery and Wildlife Biology, Colorado State University, Fort Collins, CO 80523.

Sixth FELASA Symposium on International Harmonisation of Laboratory Animal Husbandry Requirements, June 19-21, 1996. Basle, Switzerland. Contact: Kongresszentrum Messe Basle, Messeplatz 21, CH-4021 Basle, Switzerland.

2nd World Congress on Alternatives in Life Sciences, October 20-25, 1996. Utrecht, Holland. Tel: int. + 31-30-532033.

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